CHAPTER 42

Anorexia and cachexia

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Many patients with advanced cancer undergo a wasting syndrome associated with cancer anorexia/cachexia and asthenia. In a study that looked at symptoms in cancer patients being entered on a palliative care service, anorexia/cachexia and asthenia were more common problems than were pain or dyspnea. Patients who exhibit such symptoms generally have a short survival, respond poorly to cytotoxic agents, and suffer from increased toxicity from these agents.

In addition, cancer anorexia/cachexia is oftentimes associated with weakness, fatigue, and a poor quality of life. This problem not only affects the patient but also frequently has an impact on family members, as the patient is no longer able to participate fully in eating as a social activity.

Diagnostic criteria

Although some authors have tried to define criteria for diagnosing cancer cachexia, in general, it is not difficult to identify affected patients. In North Central Cancer Treatment Group (NCCTG) research trials involving more than 2,500 patients, simple criteria for anorexia/cachexia have been used:

- a 5-lb weight loss in the preceding 2 months and/or an estimated daily caloric intake of < 20 calories/kg
- a desire by the patient to increase his or her appetite and gain weight
- the physician's opinion that weight gain would be beneficial for the patient

Management

Nutritional counseling

Nutritional counseling, as provided by written materials, dietitians, physicians, and nurses, has been recommended, although its value has not been well demonstrated. Recommendations typically include eating frequent, small meals (as opposed to large meals), consuming larger quantities of food in the morning than in the evening, and avoiding spicy foods. Patients may do better if they are not exposed to the aroma of cooking. Although the benefits of such nutritional counseling are clearly limited, it does appear reasonable to provide.

There is new interest in inhibitors of tumor necrosis factor (TNF), also known as cachectin, as targeted therapy for patients with anorexia and cachexia. Agents under study include thalidomide (Thalomid) and the monoclonal antibodies etanercept (Enbrel) and infliximab (Remicade). Results from studies of these agents should hopefully be available over the next few years.

Appetite stimulants

Corticosteroids were the first agents to undergo placebo-controlled, double-blind evaluation for possible use in cancer cachexia. The first such trial, conducted in the 1970s by Moertel and colleagues at the Mayo Clinic, demonstrated that corticosteroids can stimulate appetite in patients with advanced, incurable cancer. Several subsequent placebo-controlled trials, using various steroid preparations and doses, have confirmed these results.

Dexamethasone (3-8 mg/d) is a reasonable option for clinical use. Known detriments to corticosteroid use include the well-known toxicities associated with chronic administration, including myopathy, peptic ulcer disease, infection, and adrenal suppression. Many patients with advanced cancer anorexia and cachexia, however, do not survive long enough to suffer from these toxicities.

Progestational agents Several placebo-controlled, double-blind clinical trials have demonstrated that progestational agents, such as megestrol acetate and medroxyprogesterone acetate, can lead to appetite stimulation and weight gain in patients with anorexia and cachexia. These trials also demonstrated that the effect of these drugs is seen in a matter of days and that they are effective antiemetics.

Although high doses of progestational agents can cause adrenal suppression because of their mild corticosteroid-type activity (a phenomenon not well understood by many clinicians), they do not appear to cause many of the side effects attributable to classic corticosteroids (such as peptic ulcer disease, myopathy, and opportunistic infections). In lieu of this adrenal suppression, however, stress doses of corticosteroids may be necessary in patients with trauma or infection or in surgical patients while on progestational agents. On the other hand, progestational agents increase the risk of thromboembolic phenomena–a side effect that is not seen with classic corticosteroids.

A dose-response study with megestrol acetate demonstrated a positive correlation between appetite stimulation and increased megestrol acetate doses, as doses ranged from 160 to 800 mg/d. Nonetheless, given that appetite stimulation has been demonstrated with megestrol acetate doses as low as 240 mg/d, much lower doses are used by many physicians, based primarily on cost considerations.

In the United States, a liquid formulation of megestrol acetate is considerably less expensive than the tablet form, and, milligram for milligram, the liquid preparation is more bioavailable. It is reasonable to start with 400 mg/d of liquid megestrol acetate, titrating this dose upward (maximum, 800 mg/d) or downward based on clinical response or the emergence of side effects.

A randomized, prospective clinical trial comparing the utility of megestrol acetate (800 mg/d) with dexamethasone (0.75 mg qid) demonstrated similar

effects of these medications on patients' appetites but different toxicity profiles. Whereas megestrol acetate was associated with a higher incidence of thromboembolic phenomena, dexamethasone was associated with more myopathy, cushingoid body changes, and peptic ulcers.

A double-blind clinical trial comparing an eicosapentaenoic acid (EPA)-enhanced nutritional supplement vs megestrol acetate vs both agents was recently published by the North Central Cancer Treatment Group (NCCTG). Megestrol acetate produced better results with regard to appetite stimulation than the EPA-enhanced nutritional supplement, and EPA did not appear to provide any additional benefits when compared with megestol acetate (*Jatoi A, Rowland K, Loprinzi CL, et al: J Clin Oncol 22:2469-2476, 2004*).

Other agents Various other drugs have been evaluated definitively for the treatment of cancer anorexia and cachexia and have been demonstrated to provide little or no benefit. These drugs include fluoxymesterone, pentoxifylline, hydrazine sulfate, dronabinol (Marinol), cyproheptadine, and eicosapentaenoic acid (EPA). Of note, however, the antiserotonergic drug cyproheptadine does appear to be a relatively strong appetite stimulant in patients with the carcinoid syndrome, presumably because it directly counteracts the large amounts of serotonin secreted in these patients.

EPA has been tested extensively for cancer anorexia and cachexia. Although preliminary studies had claimed improvement in appetite, body composition, and survival with EPA, these favorable findings have not been borne out in subsequent phase III trials. A total of three recently completed phase III trials have shown that EPA does relatively little for cancer anorexia and cachexia when tested in the setting of either EPA vs placebo or EPA vs megestrol acetate (see sidebar).

A number of other drugs have been evaluated in a pilot fashion for the treatment of cancer anorexia and cachexia. They include branched-chain amino acids, thalidomide (Thalomid), metoclopramide, oxandrolone (Oxandrin), and adenosine triphosphate. It is hoped that new information will be available in the near future to shed light on the possible therapeutic roles of these agents.

Enteral or parenteral nutrition

Despite the demonstrated efficacy of corticosteroids and progestational agents in patients with cancer anorexia and cachexia, these drugs do not have a major long-term impact on the vast majority of such patients. Consequently, other treatment approaches, such as enteral or parenteral nutritional methods, have been studied extensively. Several randomized trials failed to demonstrate that these nutritional approaches improve either quantity or quality of life. As a result, experts generally agree that the routine use of parenteral or enteral nutrition cannot be justified in patients with advanced cancer anorexia and cachexia.

There are, however, relatively rare circumstances in which parenteral nutrition may play a role in patients with advanced cancer. Such circumstances have been documented by case reports and small case series of patients. For ex-

ample, patients with GI insufficiency due to surgery, radiation therapy, or abdominal carcinomatosis (without impending failure of other organs) may be appropriate candidates for parenteral nutrition.

Prophylactic therapy

Given the positive impact of corticosteroids and progestational agents on cancer anorexia and cachexia and the fact that many patients with advanced cancer die with, and/or of, inanition, the potential prophylactic use of these agents was evaluated. A double-blind trial was conducted in which patients with newly diagnosed extensive-stage small-cell lung cancer were randomized to receive megestrol acetate or placebo along with standard chemoradiation therapy. This trial was unable to demonstrate any beneficial effect of megestrol acetate on treatment response, quality of life, or survival.

Thus, patients should not be treated prophylactically for cancer anorexia and cachexia outside a clinical trial. Rather, such treatment should be reserved for patients in whom anorexia and cachexia are patient-determined, symptomatic clinical problems.

Nutrition as it relates to end-of-life care

Anorexia and cachexia are major problems for many oncology patients as they approach the final stage of life. Family members are generally more distressed than the patients if/when appetite stimulants do not provide relief. Questions commonly arise about giving enteral or parenteral nutrition or "forcing" patients to consume more calories in the belief that they would feel better, get stronger, and live longer. A small measure of appropriate education, noting that the intake of more calories does not appear to have a clinical benefit, provides substantial relief. It is worthwhile to note that patients randomized to receive total parenteral nutrition or appetite stimulants (such as megestrol acetate) do not live any longer than do control patients and that "force-feeding" is not in the patients' best interests.

SUGGESTED READING

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